ESC European Society of Cardiology

European Heart Journal (2020) **41**, 2128–2129
doi:10.1093/eurheartj/ehaa451

Renin–angiotensin system and SARS-CoV-2 infection: there is a before and after

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Online publish-ahead-of-print 20 May 2020

This commentary refers to 'Renin–angiotensin–aldosterone system dysregulation and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection', by T.-J. John and K. John, 2020;doi:10.1093/eurheartj/ehaa423.

We thank Drs John and John for their comment and insights into the interplay of angiotensin II, the angiotensin II type 1 receptor, and angiotensin-converting enzyme 2 (ACE2) in an activated state of the renin–angiotensin system (RAS), as is currently proposed to occur during the course of coronavirus disease (COVID)-19.[1] Indeed, focusing on the 'after' of infection, two reports recently became available, which retrospectively analysed the outcome of COVID-19 in relation to ACE-inhibitor (ACE-I) or angiotensin II type 1 receptor blocker (ARB) intake during hospitalization of patients with a history of hypertension. One multicentre analysis including 1128 hypertensive patients, of whom 188 were receiving ACE-Is or ARBs, showed significantly lower all-cause mortality in patients on ACE-I or ARB therapy compared with those who were not (unadjusted and adjusted).[2] Another, smaller single-centre study, which included 362 hypertensive patients, of whom 115 were taking ACE-Is or ARBs, reported similar disease severity and survival in patients with and without an ACE-I or ARB (unadjusted only).[3] These observations suggest at the least no harm by continuing RAS inhibitory therapy in patients with COVID-19 according to current guidelines for the treatment of cardiovascular diseases. However, prospective randomized trials are still needed to demonstrate or refute a potential protective effect of ACE-I or ARB therapy in COVID-19 patients with no established ACE-I or ARB indication.

Then there is also the 'before' of infection. Similarly unsolved, but with even less to no available data, is the question of whether use of an ACE-I or ARB affects the susceptibility for SARS-CoV-2 infection or the organ-specific dissemination of the virus. In a recent large-scale study using single-cell RNA sequencing data, age, male gender, and smoking were associated with higher expression of ACE2 and of the proteases necessary for cellular entry of SARS-CoV-2 in airway (age, gender, and smoking) and type II alveolar epithelial cells (age and gender).[4] These data now strongly support that the expression pattern of ACE2 and of the accompanying proteases can mirror key observations made in connection with the epidemiology and clinical presentation of COVID-19. It will therefore be of major interest to determine whether cardiovascular diseases *per se*, and/or their treatment with ACE-Is or ARBs, are associated with a similar cell type-specific enhancement of the molecular toolkit required for viral cell entry. If this were the case, a causal relationship with the susceptibility to infection with SARS-CoV-2 and the severity of the COVID-19 disease would have to be further investigated.

Currently, new observations and data on COVID-19 are made available at a fast pace, many even before having been peer reviewed. We certainly have to stay on the outlook for new and solid evidence, which can be integrated into our just emerging understanding of SARS-CoV-2 infection and COVID-19.

Conflict of interest: none declared.

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